

**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

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*Ex parte* JAMES R. LADINE, IAN JARDINE, and MIKE S. STORY

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Appeal 2007-4155  
Application 09/835,273  
Technology Center 1600

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Decided: December 14, 2007

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Before DONALD E. ADAMS, ERIC GRIMES, and JEFFREY N.  
FREDMAN, *Administrative Patent Judges*.

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**DECISION ON APPEAL**

This is an appeal under 35 U.S.C. § 134 involving claims to a method of analysis of proteins using parallel mass spectrometric techniques which the Examiner has rejected on grounds of obviousness. We have jurisdiction under 35 U.S.C. § 6(b). We reverse and enter new grounds of rejection.

## BACKGROUND

“[W]ithin a typical cell there are several thousand proteins, its ‘proteome,’ which carry out the metabolic work of the cell” (Specification 1). The Specification discloses that “analysis of the abundance of proteins can therefore be useful in elucidating the molecular basis of differences brought about by diseases or by therapeutic treatments” (Specification 1). The Specification states “[a] number of techniques have been suggested for analyzing cellular proteins, including, for example, two-dimensional electrophoresis followed by mass spectrometry” (Specification 1).

The Specification states “[a]n object of this invention is to achieve analysis of a large number of proteins in an accurate, time-effective manner” (Specification 2). The Specification discloses that “[s]tudies of massive numbers of proteins in short time intervals can be achieved accurately and in a time effective manner by employing a coordinated array of mass spectrometry systems” (Specification 4).

## STATEMENT OF THE CASE

### *The Claims*

Claims 1-2, 5-18 and 22-45 are on appeal. The claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

We will focus on claims 1 and 29 which are representative and read as follows:

1. A method for analysis of proteins in a biological system comprising:  
providing a biological system;

sampling the biological system at multiple time intervals to provide multiple samples, each sample containing multiple proteins;

submitting each of the multiple samples to a separation technique to provide multiple protein samples suitable for analysis by mass spectrometry; and

analyzing the multiple samples to determine changes in abundance of proteins as a function of time, said analyzing including

allocating the multiple protein samples for the multiple samples among mass spectrometry systems in a parallel array of mass spectrometry systems, each mass spectrometry system analyzing a different one of the multiple protein samples and providing mass spectral data indicating identity and abundance of one or more proteins,

directing mass spectral data from each of the mass spectrometry systems in said array to a common computing device, and

collating said mass spectral data from each of the mass spectrometry systems as a function of time of sampling of the biological system.

29. A system for mass spectrometric analysis of proteins in a biological system, the system comprising:

a parallel sample separation apparatus adapted to receive multiple samples of a biological system taken at multiple time intervals, and separate the multiple samples in parallel to obtain multiple protein samples for analysis by mass spectrometry;

a parallel array of mass spectrometry systems adapted to receive the multiple protein samples from the separation apparatus and analyze the multiple protein samples in parallel to generate mass spectral data indicating identity and abundance of proteins, each mass spectrometry system analyzing a different one of the multiple protein samples; and

a computing device communicating with the parallel array of mass spectrometry systems and the parallel

separation apparatus, the computing device being adapted to analyze the mass spectral data from the parallel array of mass spectrometry systems and collate the mass spectral data as a function of time of sampling.

The Examiner has rejected claims 1-2, 5-18 and 22-45 under 35 U.S.C. § 103(a) based on:

Zenhausen et al. US 2002/0094531, June 14, 1999 (hereafter “Zenhausen”).

Demirev et al. “*Probing Combinatorial Library Diversity by Mass Spectrometry*” 69 Anal. Chem. 2893-2900 (01 August 1997) (hereafter “Demirev”).

Zeng et al. “*Developments of a Fully Automated Parallel HPLC/Mass Spectrometry System for the Analytical Characterization and Preparative Purification of Combinatorial Libraries*” 70 Anal. Chem. 4380-4388 (15 October 1998) (hereafter “Zeng”).

Henry et al. “*The Incredible Shrinking Mass Spectrometers*” Analytical Chemistry News & Features 264A-268A” (1 April 1999) (hereafter “Henry”).

Cotter et al. “*Miniaturized Time-of-Flight Mass Spectrometer for Peptide and Oligonucleotide Analysis*” 34 J. Mass Spectrom. 1368-1372 (1999)(hereafter “Cotter”).

Orient et al “*Miniature, High-Resolution, Quadrupole Mass-Spectrometer Array*” 68(3) Rev. Sci. Instrum. 1393-1397 (March 1997) (hereafter “Orient”).

Chalmers et al “*Advances in Mass Spectrometry for Proteome Analysis*” 11 Current Opinion in Biotechnology 384-390 (2000)(hereafter

“Chalmers”).

*The Issue*

The Examiner has written two different 103 rejections, but both rejections rely upon the Zenhausern, Demirev and Zeng references, with the second rejection adding the Chalmers, Henry, Cotter and Orient references.

In the first rejection the Examiner contends that Zenhausern teaches monitoring biomolecules in a sample with a plurality of detection devices where the biomolecules can be proteins and the devices can be mass spectrometers (Answer 3). The Examiner acknowledges that Zenhausern does not teach preparing the sample using a separation technique (Answer 4). The Examiner relies upon Demirev to teach the preparative step (Answer 4). The Examiner relies upon Zeng to teach multiplexing the mass spectrometric device, though recognizing that Zeng uses a single mass spectrometer (Answer 5).

In the second rejection, the Examiner adds to the combination of Zenhausern, Demirev and Zeng that Chalmers teaches profiling multiple constituents (Answer 6). The Examiner cites the Henry, Cotter and Orient references to show that small, light weight mass spectrometers are available which could be multiplexed as suggested by Zenhausern (Answer 8).

Appellants respond to the first obviousness rejection, arguing that “Zenhausern does not teach that its multisensor array can be used to conduct parallel analysis of different samples (i.e., where each sensor of the array senses a different sample, protein or otherwise), nor does it suggest how the array may be modified to do so” (App. Br. 5). Appellants also argue that

there is no reason, motivation or suggestion in the prior art to analyze multiple samples in a parallel fashion (App. Br. 6).

Appellants raise similar arguments to the second obviousness rejection, contending that there is no teaching by Demirev or Chang of an array of mass spectrometric systems which identify protein identity and abundance (see App. Br. 6). Appellants argue that

[n]one of the cited prior art references describe the architecture and workflow embodied in the independent claims of the present invention, whereby multiple samples are allocated among individual mass spectrometer systems of an interconnected array such that each sample is analyzed by a different mass spectrometer system. Furthermore, general knowledge that analytical devices can be combined does not in and of itself suggest the claimed architecture or workflow.

(App. Br. 7). Appellants dismiss the remaining references (Henry, Cotter, and Orient) as simply teaching miniaturized or simplified single mass spectrometers which do not teach formation of a multiplex system (App. Br. 8).

In view of these conflicting positions, we frame the issue before us as follows:

Do the cited references teach a method and device for sampling a biological system at multiple time intervals to provide multiple samples where each sample contains multiple proteins, using a parallel sample separation apparatus linked to a parallel array of mass spectrometers which communicate with a computing device?

## DISCUSSION

“In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant.” *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993).

We agree with the Appellants that the cited references do not teach a step of sampling the biological system at multiple time intervals to provide multiple samples with multiple proteins. The Examiner contends that Zenhausern teaches a time change in the accumulation of PCR products that renders the claimed step obvious (Answer 9). However, even extending this teaching as broadly as possible, the sampling of the PCR reaction does not provide multiple samples with multiple proteins (*see* Zenhausern, figure 2 and page 8, paragraph 0076). The Examiner also points to the analysis of Edman degradation products as supporting the sampling step (*see* Answer 4). However, Edman degradation products are not biological samples that will undergo changes in protein abundance over time, as required by the claims. *See, e.g., CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (“obviousness requires a suggestion of all limitations in a claim”).

We also agree with Appellants that the Zenhausern reference, viewed without the benefit of hindsight, would not have suggested a parallel array of mass spectrometers to a person of ordinary skill in the art. In our view, the Examiner has not accurately characterized the teachings of Zenhausern. The passage referenced by the Examiner reads as follows:

The n number of sensing probes can be a multiple sensor array. The n number of sensing probes can also be at least one semiconductor gas sensor, doped metal oxide gas sensor or an undoped metal oxide gas sensor used in gas or vapor phase, conductive polymer sensor, vibrating or resonant micromechanical device, mass spectrometer, or optical sensing probe (e.g., an optical fiber, apertured probe, and/or apertureless probe). The sensing probe can also have one or more coatings.

(Zenhausern at 5, paragraph 0047).

The Examiner characterizes this passage as teaching that the “n number of sensing probes is an array of mass spectrometers” (Answer 3). While Zenhausern clearly contemplates a sensor array, we do not agree that the cited passage from Zenhausern would have suggested to those skilled in the art that the array have multiple mass spectrometers. *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (“[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness”).

Therefore, we conclude that the Examiner has not made out a prima facie case of obviousness with respect to the claimed process. The rejection of claims 1-2, 5-18 and 22-45 over the combined teachings of Zenhausern, Demirev, Zeng, Henry, Cotter, and Orient is reversed.

#### *New grounds of rejection*

Under the provisions of 37 C.F.R. § 41.50(b), we enter the following new grounds of rejection.



Claims 1-2, 5-16, 18, 22-25, 27-32 and 34-45 are rejected under 35 U.S.C. § 103 as obvious in view of Easterling et al., 70 Anal. Chem. 2704-2709 and Krutz (U.S. Patent 3,624,420), Zeng, Demirev and Nordhoff et al., 17 Nature Biotechnology 884-888.

Easterling teaches a method (claim 1) and device (claims 22 and 29) for analysis of proteins in biological systems (Easterling at 2705, col. 1, ll. 22-32) comprising:

sampling the biological system at multiple time intervals to provide multiple samples, each sample containing multiple proteins (Easterling at 2707, col. 2, ll. 7-13, “the time-dependence of protein expression may be examined by sampling the fermentation at regular intervals after induction”),

analyzing the multiple samples to determine changes in abundance of proteins as a function of time (Easterling at 2707, col. 2, ll. 16-20, “The abundance of the target protein relative to that of the native *E. coli* protein collected at four times during the induction is shown in Table 2.”),

including allocating the multiple protein samples for the multiple samples on a mass spectrometry system (Easterling at 2705, last paragraph to page 2706), and

collating said mass spectral data from the mass spectrometry system as a function of time of sampling of the biological system (Easterling at 2708, Table 2).

With regard to claims 2 and 45, Easterling teaches displaying data as a function of protein identity, protein abundance and time (Easterling at 2708, Table 2, where the protein PfRd is shown with values for its intensity at different times after induction).

With regard to claim 12, Easterling teaches proteolytic cleavage for protein analysis (Easterling at 2709, col. 2).

With regard to claims 14-16, 18, 43, and 44, Easterling teaches comparison of a biological system that is stimulated by induction with IPTG with a zero time point and one hour time point and correlating the mass spectral data separately and inferring IPTG responsiveness (Easterling at 2708, Table 2).

With regard to claim 32, Easterling teaches a computing device which collates the mass spectral data as a function of time (*see* Easterling at 2708, table 2).

Easterling does not teach two elements of claim 1. Easterling does not teach the “parallel array of mass spectrometry systems, each mass spectrometry system analyzing a different one of the multiple protein samples and providing mass spectral data indicating identity and abundance of one or more proteins.” Easterling also does not teach “submitting each of the multiple samples to a separation technique to provide multiple protein samples suitable for analysis by mass spectrometry.”

Krutz teaches a parallel array of mass spectrometers, where each mass spectrometer analyzes a different sample (Krutz, figure 1 and col. 4, ll. 45-60).

With regard to claims 5, 25, 34, and 35, Krutz notes that the “invention can be used to control more or fewer than three spectrometers and the number shown was chosen for example purposes only” (Krutz, col. 3, lines 14-18).

Zeng teaches submitting multiple samples to a separation technique to provide samples suitable for analysis by mass spectrometry, specifically a parallel HPLC and mass spectrometry system (Zeng at 4382, col. 1 and figures 1 and 2).

With regard to claims 8-9, 11, 13, 24, 31, and 37-39, Zeng teaches the use of parallel liquid chromatography apparatus (specifically HPLC) which are controlled by a single computing device (Zeng at 4381, column 2). Zeng teaches that these separation apparatus treat multiple samples in parallel using the LC/MS systems (Zeng at 4381, column 1).

With regard to claims 6-7, 27, 36, and 41-42, Demirev teaches that analysis of several thousand peptides is feasible using mass spectroscopy (Demirev at 2900, col. 2). Demirev analyzes mixtures of 20 to more than 8,855 peptides (Demirev at 2896, table 1).

With regard to claims 10, 23, 28, 30, and 40, Nordhoff teaches a single magnetic particle separation device which functions to separate proteins prior to mass spectrometry on a single mass spectrometer (Nordhoff at 887, col. 1 and 2, subheading “Dynabead purification”).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the multiplex mass spectrometric array of Krutz and the presample preparation techniques of Zeng, Demirev and Nordhoff in the mass spectrometric analysis method of Easterling. Motivation to use multiple mass spectrometers is provide by Krutz, who notes, “the cost of apparatus embodying the invention, with the capacity to control three spectrometers, is about half the cost of comparable prior art systems” (Krutz, col. 2, ll. 27-30).

Further motivation to prepare the samples using the preparative methods is provided by Nordhoff, who comments that the

solid support is well suited for high-throughput applications and the necessary instrumentation is commercially available. The use of paramagnetic particles is especially efficient for large scale screenings in which numerous samples can be examined in parallel using different binding and washing conditions . . . However, the power of MALDI-TOF MS peptide mapping for identification of posttranslational modifications and the possibility of analyzing multiprotein complexes add a new dimension to such experiments.

(Nordhoff at 887, col. 1).

In accord is Zeng, who teaches “[o]ur parallel analytical/preparative HPLC/MS is the first mass spectrometry-based system that permits automated and rapid characterization and purification of compound libraries in a parallel manner, thus providing a better ‘match’ for high-throughput parallel synthesis” (Zeng at 4387, col. 2 to 4388 col. 1).

In *KSR Int’l v. Teleflex*, the Supreme Court, in rejecting the rigid application of the teaching, suggestion, and motivation test by the Federal Circuit, indicated that

The principles underlying [earlier] cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability.

*KSR Int’l v. Teleflex Inc.*, 127 S. Ct. 1727, 1740 (2007).

Applying the *KSR* standard of obviousness to Easterling, Krutz, Nordhoff, Demirev, and Zeng, we conclude that the combination of multiple mass spectrometers, as taught by Krutz, to analyze multiple proteins at multiple times as taught by Easterling, with preparative steps taught by Nordhoff and Zeng, represents a combination of known elements which yield the predictable result of permitting high throughput analysis of protein samples. The use of multiple linked mass spectrometers as taught by Krutz in this combination would further serve to achieve the predictable result of high throughput analysis, since the more components that are linked in parallel, the larger the number of samples which can be subjected to analysis. Such a combination is merely a “predictable use of prior art elements according to their established functions.” *KSR Int’l*, 127 S. Ct. at 1740.

Claims 17 and 26 are rejected under 35 U.S.C. § 103 as obvious in view of Easterling et al., 70 Anal. Chem. 2704-2709 and Krutz (U.S. Patent 3,624,420), Zeng, Demirev, Nordhoff et al., 17 Nature Biotechnology 884-888 and Valenzuela et al. (U.S. Patent 5,814,478).

Claims 1, 2, 5-16, 18, 22-25, 27-32 and 34-45 are rejected for the reasons given above. The two dependent claims, 17 and 26, include the further limitation of analyzing biological systems in the ranges of 5 to 60 seconds and 5 to 10 minutes, respectively, which is a range shorter than that taught by Easterling.

Valenzuela teaches regarding the activation of a protein by its ligand that “induction was detectable by one minute, peaked within the first five

minutes, and remained elevated for over an hour” (Valenzuela, col. 33, ll. 16-18).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to analyze the protein induction of Valenzuela over the time frame of Valenzuela using the method and system of Easterling, Krutz, Zeng, Demirev and Nordhoff in order to obtain the advantages noted by Easterling that “MALDI-TOF mass spectrometry has been successfully applied to direct, rapid, offline analysis of protein synthesis by bacterial overexpression. This analysis furnishes simple verification of induction success or failure and has been shown to be effective for the analysis of various proteins over a wide mass range” (Easterling at 2709, col. 1).

Applying the *KSR* standard of obviousness to using the protein and times of Valenzuela with the method of Easterling, Krutz, Demirev, Nordhoff, and Zeng, we conclude that claims 17 and 26 are directed to a combination of known elements which yield the predictable result of permitting high throughput analysis of protein samples. Such a combination is merely a “predictable use of prior art elements according to their established functions.” *KSR Int’l*, 127 S. Ct. at 1740.

Claim 33 is rejected under 35 U.S.C. § 103 as obvious in view of Easterling et al., 70 Anal. Chem. 2704-2709 and Krutz (U.S. Patent 3,624,420), Zeng, Demirev, Nordhoff et al., 17 Nature Biotechnology 884-888 and Koster et al. (U.S. PGPUB 2002/0009394).

Claims 1, 2, 5-16, 18, 22-25, 27-32 and 34-45 are rejected for the reasons given above. Dependent claim 33 includes the further limitation of analyzing data using a graphical user interface.

Koster teaches

to evaluate test samples until the test run parameters are changed by the APL operator. As noted above, a test run might involve producing mass spectrometer output and analyzing it on a 24-hours-per-day basis. In the preferred embodiment, the operator provides the test run parameters through a graphical user interface using a display mouse and keyboard of the APL system.

(Koster at 11, paragraph 0130).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to analyze the data generated using the method of Easterling, Krutz, Zeng, Demirev and Nordhoff with the graphical user interface of Koster since graphical user interfaces are preferred as simple ways to interact with the devices.

Applying the *KSR* standard of obviousness to using graphical user interface of Koster with the method of Easterling, Krutz, Demirev, Nordhoff, and Zeng, we conclude that claim 33 is directed to a combination of known elements which yield the predictable result of permitting high throughput analysis of protein samples. Such a combination is merely a “predictable use of prior art elements according to their established functions.” *KSR Int’l*, 127 S. Ct. at 1740.

#### CONCLUSION

This decision contains new grounds of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12,

2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the Appellants, *WITHIN TWO MONTHS FROM THE DATE OF THE DECISION*, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

(1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the Examiner, in which event the proceeding will be remanded to the Examiner. . . .

(2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

REVERSED, 37 C.F.R. § 41.50(b)

lp

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